UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

June 7, 2022

MEMORANDUM

SUBJECT: Updated Uses and Usage of Triazole and Demethylation Inhibitor (DMI) Fungicide Pesticides

FROM: Lindsey Hendrick, Biologist
Science Information and Analysis Branch
Biological and Economic Analysis Division (7503M)

THRU: Hope Johnson, Chief
Science Information and Analysis Branch
Biological and Economic Analysis Division (7503M)

TO: Cynthia Giles-Parker, Chief
Fungicide Branch
Registration Division (7505M)

Susan Jennings, Senior Advisor for Public Health
Office of the Director
Office of Pesticide Programs (7501M)

BEAD Product Review Panel Date: May 11, 2022

SUMMARY

In 2017, the Centers for Disease Control and Prevention requested that the Office of Pesticide Programs provide information related to the use and usage of the triazole fungicides and other demethylation inhibitor (DMI) fungicide pesticides to inform epidemiological investigations of the origins of clinical triazole resistance in *Aspergillus fumigatus*. This information was presented in Suarez et al. (2018). The Centers for Disease Control and Prevention has requested updated triazole and other DMI fungicide use and usage information, which is summarized herein. The Biological and Economic Analysis Division found that agricultural usage of the DMI fungicides has increased, in terms of pounds of active ingredient applied and total acres treated, while usage in the consumer sector has decreased substantially, since publication of Suarez et al. (2018). These data alone are not sufficient to link triazole resistance in *A. fumigatus* to any pesticidal use or uses. Rather, the information is intended to inform epidemiological investigations into the origins of clinical triazole resistance in *A. fumigatus*.

INTRODUCTION

Triazole and other demethylation inhibitor (DMI) fungicides are registered as pesticides on a wide variety of use sites ranging from agricultural crops and turf to wood decay prevention treatments and paint additives. Some chemicals in this class also have important uses as human and veterinary drugs (Hagiwara et al. 2016, Verweij et al. 2016, Doki et al. 2020, Guillot and Bond 2020). This creates a potential for use of DMI and triazole pesticidal active ingredients in agriculture to contribute to or cause development of resistance in fungi of clinical importance in humans. One fungus with such potential is *Aspergillus fumigatus*. *Aspergillus fumigatus* is a ubiquitous saprophytic fungus found in both soil and air. This fungus is a facultative human pathogen, which is treated with clinical triazoles.

Resistance to clinical triazoles has long been documented in *A. fumigatus* (Denning et al. 1997). Some authors have hypothesized that resistance may be the result of non-clinical triazole usage (*e.g.*, Kano et al. 2014, Ribas et al. 2016, Garcia-Rubio et al. 2021). Specifically, authors have postulated that agricultural and floricultural use of triazole pesticides could be responsible for the presence of certain strains of triazole-resistant *A. fumigatus* in the environment (*e.g.*, Chowdhary et al. 2013, Berger et al. 2017). Hence, the Centers for Disease Control and Prevention (CDC) is engaged in an epidemiological investigation of the role of agricultural use of triazole pesticides in the emergence and spread of triazole-resistant *A. fumigatus*.

In 2017, CDC requested that the Office of Pesticide Programs (OPP) provide information related to triazole use and usage to support this research. Suarez et al. (2018) summarized available triazole and DMI fungicide use and usage information for the United States between 2006 and 2016. Triazoles are only one of six chemical groups of DMI fungicides, the others being piperazines, pyridines, pyrimidines, imidazoles, and triazolinthiones. Available data for DMI fungicides across these six classes were summarized because resistance to clinical triazoles has been documented in the triazoles and active ingredients in other DMI classes (Cools et al. 2013). The DMI fungicides inhibit sterol biosynthesis in fungi. Several resistance mechanisms have been identified across fungal species (FRAC 2022). While the level of cross-resistance between DMI fungicides is undetermined, FRAC recommends treating individual phytopathogens exhibiting resistance as cross-resistant to the group (FRAC 2022). For this reason, information is presented for all DMI fungicide classes registered in the United States, rather than the triazoles alone, both in Suarez et al. (2018) and herein.

The Centers for Disease Control and Prevention has requested that Suarez et al. (2018) be updated to inform an upcoming National Academies of Sciences workshop focused on the role of agricultural fungicides in the development of antimicrobial resistant microbes affecting human health and to provide continued support for the epidemiological investigation. This memorandum summarizes the use and usage data for the triazole and other DMI fungicides published after Suarez et al. (2018) and identifies changes in use and usage that have occurred, when data are available to make such comparisons. Usage data trends evaluated herein include acres treated, pounds of active ingredient applied, and application rates. While comparisons of pounds applied across active ingredients are generally discouraged due to differences in biological activity and, as a result, efficacious application rates between active ingredients, consistency in the usage of the individual DMI fungicide active ingredients applied to use sites between the two reporting periods makes high level comparisons possible in this case. However, these comparisons should be viewed only as very general indicators of changes in usage with further analysis required to fully understand changes in DMI usage. CDC has requested an overview of total triazole use and usage and EPA finds the data are appropriate for this level of comparison. Therefore, EPA is providing characterization of usage at the mode of action (MOA) level, *i.e.,* encompassing each of the DMI fungicides.

METHODOLOGY

Pesticide use refers to the sites at which a pesticide may legally be applied and associated use restrictions, according to the product registration whereas usage data reflect real world applications of a pesticide. Analysts reviewed active product registrations for the registered triazole and relevant additional DMI active ingredients to provide an overview of the types of registered uses for each active ingredient. While every individual use per active ingredient is not specified, the uses outlined herein contextualize the types of uses (*e.g.,* field crops, orchard crops, ornamental plants) for which each active ingredient is registered.

Overall usage of DMI fungicides was compared between the reporting period of 2011 to 2015 and the most recent five years of available data (*i.e.,* 2016 to 2020) for the purpose of identifying general trends in DMI fungicide usage. Importantly, the usage values presented in Suarez et al. (2018) included seed treatment data which are no longer supported by the data provider. Because those data are not supported, the Agency compares only foliar and soil applications of the DMI fungicide application ingredients in this assessment. As a result, the 2011 to 2015 values presented herein are different than those reported in Suarez et al. (2018) for many active ingredients and crop uses.

Comparisons are made between base acres treated (BAT), which indicates how many unique acres of an agricultural crop are treated, total acres treated (TAT), which represents the total number of acre treatments that occurred, including multiple treatments to the same acre of cropland with an active ingredient, and pounds active ingredient (lbs AI) applied. The area treated with a specific pesticide only contributes to BAT once, therefore subsequent applications with a given pesticide do not contribute to the BAT total. Thus, BAT for a given active ingredient can be interpreted as the estimated spatial footprint of usage in the United States while TAT is indicative of the extent of usage, as multiple applications of an individual active ingredient to the same acre are reflected by this metric. Total reported pounds applied are also compared. As previously stated, while comparisons of pounds applied across active ingredients are generally discouraged, these types of comparisons were deemed appropriate for this case.

USE

Table 1 presents the EPA-registered DMI fungicides in the United States and generalized use sites associated with each active ingredient. The table does not differentiate application method (*e.g.*, seed treatment, post-harvest application). It is important to note that the use sites listed in Table 1 are not exhaustive but are indicative of the type and range of uses registered for each active ingredient. End-use product registrations that specify all active registered uses for a pesticide product can be queried using the Environmental Protection Agency's Pesticide Product and Label System.[1]

The EPA-registered triazole fungicides are bromuconazole, cyproconazole, difenoconazole, fenbuconazole, flutriafol, ipconazole, metconazole, myclobutanil, propiconazole, tebuconazole, tetraconazole, triadimefon, triticonazole, and mefentrifluconazole, a new triazole active ingredient registered in 2019 for food and non-food uses. Additional EPA-registered non-triazole DMI fungicides evaluated herein are prothioconazole, triforine, imazalil, and triflumizole. As noted in Suarez et al. (2018), all fenarimol registrations were cancelled in 2012. However, the cancellation order stipulates that fenarimol users may exhaust existing stock and usage has been reported in recent years. The sole triforine end-use product registration was cancelled in 2018 and there are no active triadimenol registrations, however, like fenarimol, continued usage may occur as existing stocks are depleted.

There have been several changes to the registered uses of the DMI fungicides since Suarez et al. (2018). Current registered uses of the active ingredients are summarized in Table 1. New uses since the previous assessment are indicated by a gray cell with an 'N' notation.

[1] The Pesticide Product and Label System (PPLS) provides a collection of pesticide product labels that have been accepted by EPA under Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Table 1. Registered uses of triazole and DMI fungicide active ingredients in the United States.

Use Site[1] \ Active Ingredient	Bromuconazole	Cyproconazole	Difenoconazole	Fenbuconazole	Flutriafol	Ipconazole	Metconazole	Myclobutanil	Propiconazole	Tebuconazole	Tetraconazole	Triadimefon	Triadimenol[2]	Triticonazole	Fenarimol[3]	Mefentrifluconazole	Prothioconazole	Triforine[3]	Imazalil	Triflumizole
AGRICULTURAL CROPS																				
FRUITS																				
Citrus Fruits (e.g., orange, lemon, lime, grapefruit, etc.)			X	X					X							N			X	
Pome Fruits (e.g., apple, pear, quince, etc.)			X	O	X			O	O	X						N				X
Stone Fruits (e.g., apricot, cherry, peach, plum, etc.)			X	X	X		X	O	X	X						N				O
Berries and Small Fruit			O	O	O		O	O	O	O	O					N	X			O
Caneberries (e.g., blackberries and raspberries)								O	X							N				
Bushberries (e.g., blueberries and currants)			X	O	O		X	O	X							N	O			
Small climbing fruit vines (e.g., grapes and gooseberries)			X		O			O		X	X					N				X
Low growing berries (e.g., cranberry and strawberry)			X	O	O			O	X		X					N				O
Subtropical/Tropical Fruits (e.g., banana, mango, pineapple, etc.)			O	O				X	O	X										O
NUTS AND SEEDS																				
Tree Nuts (e.g., almond, pecan, walnut, etc.)			X	O	X		X	O	X	X	O					N				O
Oil Seeds (e.g., canola, crambe, sunflower, etc.)			O			O	O		X	O						N	O			
GRAINS																				
Cereal Grains		O	O	O	O	X	O		X	O	O			O			X			
Barley			X		N	X	X		X	X	N			X		N	X		X	
Buckwheat						X			X							N	X			

Active Ingredient / Use Site[1]	Bromuconazole	Cyproconazole	Difenoconazole	Fenbuconazole	Flutriafol	Ipconazole	Metconazole	Myclobutanil	Propiconazole	Tebuconazole	Tetraconazole	Triadimefon	Triadimenol[2]	Triticonazole	Fenarimol[3]	Mefentrifluconazole	Prothioconazole	Triforine[3]	Imazalil	Triflumizole
Corn		X	X		X	X	X		X	X	X			X		N	X			
Millet						X			O							N	X			
Oats			X			X	X		X	X				X		N	X			
Rice						X			X								X			
Rye			X			X	X		X	X				X		N	X			
Sorghum					X	X			X					X		N	X			
Triticale		X	X		X	X	X		X	X				X		N	X		X	
Wheat		X	X	X	X	X	X		X	X	N			X		N	X		X	
VEGETABLES																				
Root and Tuber Vegetables (e.g., beets, carrots, potato, radish, sweet potato, etc.)			X	O	O	X	O	O	O	O	O					N	O			
Bulb Vegetables			X						X	X						N				
Bulbs (e.g., garlic, onion, shallot)			X		X	O		O	X	O						N	O			O
Greens (e.g., leeks, green onions, etc.)			X						X	O						N				
Leafy Vegetables			N		X	X		O	O	O						N	O			O
Vegetable Stems [Leafy Petioles] (e.g., celery, rhubarb, Swiss chard, etc.)					X				X											X
Cole Crops (e.g., broccoli, cabbage, cauliflower, collards, kale, etc.)			X		X	X				O										X
Fruiting Vegetables (e.g., eggplant, okra, pepper, tomato, etc.)			X	O	X			O	O	X	N					N				O
Cucurbit Vegetables (e.g., cucumber, gourds, melons, pumpkin, squash, etc.)			X		X	X		X		X	N					N	X			X
Legumes (e.g., beans, chickpeas, lentils, peas, soybeans, etc.)		O	O	O	O	X	O	O	O	O	O					N	O			
Beans			X			O		O	O	X	N						X			

Active Ingredient / Use Site[1]	Bromuconazole	Cyproconazole	Difenoconazole	Fenbuconazole	Flutriafol	Ipconazole	Metconazole	Myclobutanil	Propiconazole	Tebuconazole	Tetraconazole	Triadimefon	Triadimenol[2]	Triticonazole	Fenarimol[3]	Mefentrifluconazole	Prothioconazole	Triforine[3]	Imazalil	Triflumizole
Garbanzos (including Chickpeas)			X			X											X			
Peanuts		X		X	X	X	X		X	X	X					N	X			
Peas and Lentils						O											X			
Soybeans		X	X		X	X	X	X	X	X	X					N	X			
UNGROUPED																				
Alfalfa					N											N	X			
Bluegrass								X												
Hops					X			X		X										X
Cotton			X		X	X	X	X		X						N	N			
Mint/Peppermint/Spearmint								X	X											
Sugarcane							X		X							N				
AGRICULTURAL PRODUCTION																				
Poultry Hatchery Premises and Equipment																			X	
Mushroom Houses - Empty Premises and Equipment									X											
ORNAMENTALS AND TURF																				
Commercial/Industrial Lawns					N				X					X		N				
Flowers			X					O	O	O				O						
Golf Course Turf			X		N		X		X	X				X		N	N			
Grasses Grown for Seed								X	X	X						N				
Nursery Stock														X			X			
Ornamentals (Unspecified)			X		N		X	X	X	X		O		X		N	O			X
Ornamental and/or Shade Trees			X		N		X	X	X	X		X		X		N				X
Ornamental Grasses			X		N		X	X	X	X				X						X
Ornamental Herbaceous Plants	O		X		N	X	X	X	X	X				X		N				X
Ornamental Lawns and Turf			X		N	X	X	X	X	X				X			X			X

Use Site[1] / Active Ingredient	Bromuconazole	Cyproconazole	Difenoconazole	Fenbuconazole	Flutriafol	Ipconazole	Metconazole	Myclobutanil	Propiconazole	Tebuconazole	Tetraconazole	Triadimefon	Triadimenol[2]	Triticonazole	Fenarimol[3]	Mefentrifluconazole	Prothioconazole	Triforine[3]	Imazalil	Triflumizole
Ornamental Nonflowering Plants			X		N		X	X	X	X				X		N				X
Ornamental Sod Farm (Turf)			X		N		X	X	X	X				X		N				X
Ornamental Woody Shrubs and Vines			X		N		X	X	X	X		X		X		N				X
Non-bearing Fruit Trees			X									X				N				X
Recreation Area Lawns					N									X						
Residential Lawns							X	X						X						
Consumer Use (e.g., lawns, ornamentals, gardens)																				
NURSERY AND FORESTRY																				
Conifers (Plantations/Nurseries)			X			X						X		X		N				
Christmas Tree Plantations			X									X		X		N				
Conifers (Seed Orchard)								O				X								
Pine Seedlings												X								
Hybrid Cottonwood/Poplar Plantations			X					X												
Forest Trees								O	X			X		X						
SPECIALTY AND INDUSTRIAL																				
Industrial Adhesives and Coatings									X	X										
Commercial/Industrial Water Cooling Systems									X											
Metalworking Cutting Fluids									X	X										
Paints (in-can)									X											
Paints, Latex/Oil/Varnish (Applied Film)									X											
Paper/Paper Products									X											
Plastic Products									X	X										
Rubber Products									X											

Use Site[1] \ Active Ingredient	Bromuconazole	Cyproconazole	Difenoconazole	Fenbuconazole	Flutriafol	Ipconazole	Metconazole	Myclobutanil	Propiconazole	Tebuconazole	Tetraconazole	Triadimefon	Triadimenol[2]	Triticonazole	Fenarimol[3]	Mefentrifluconazole	Prothioconazole	Triforine[3]	Imazalil	Triflumizole
Specialty Industrial Products									X	X										
Textiles/Textile Fibers/Cordage									X											
Wood Protection Treatment									X	X										

1 Use sites in Table 1 are not exhaustive but are indicative of the type and range of uses registered for each active ingredient. Where an 'X' is indicated, the active ingredient is registered for all or a majority of sites or crops that are described by the listed site, 'O' indicates the active ingredient is registered for only some of the use sites or crops that are described by the listed site, and 'N' indicates new registered uses of the active ingredient since 2016.
2 There are no active technical or end-use registrations for this active ingredient.
3 All technical and end-use registrations have been cancelled.

USAGE

Agricultural Usage

Analysts in the Biological and Economic Analysis Division (BEAD) of OPP evaluated the available pesticide usage data and estimated average annual usage values for the triazole and DMI fungicides. The primary usage source is Kynetec USA, Inc., an agricultural market research firm that provides annual usage estimates for approximately 60 agricultural crops at the national level. For crops not surveyed by Kynetec, these data are supplemented with national-level usage survey data from the United States Department of Agricultural National Agricultural Statistics Service (USDA NASS) that are generally collected biannually. Currently, there are no available sources of seed treatment data upon which to make reliable and quantifiable estimates of usage for triazole and DMI fungicides. The absence of such seed treatment data should not be interpreted as lack of usage. Usage data are available for many crops, but it is important to note that not all registered uses are surveyed at the national level. The Agency relies of surveys of pesticide usage that incorporate the majority of agricultural crop acreage. Crops that aren't surveyed for pesticide usage are generally those with small national acreage. Therefore, the usage estimates provided herein likely underestimate total agricultural usage. Data are presented as rounded, annual averages.

Relative usage of triazole and DMI active ingredients on the following crops was low from 2011 to 2015 (Suarez et al. 2018) and remained low from 2016-2020: apricot, artichoke, asparagus, avocado, succulent beans (snap, bush, pole, green), blueberries, broccoli, cabbage, caneberries (including raspberries), carrots, cauliflower, celery, cucumber, hazelnuts, honeydew melon, lemon, lettuce, lima bean, onion, pepper, pumpkin, nectarine, spinach, squash, tangerine (Kynetec 2021, USDA NASS 2022). DMI fungicide usage on hazelnut and garlic remained stable during this time (Kynetec 2021). Additionally, while spinach and tobacco are surveyed, no usage of any DMI fungicides has been reported for these crops since publication of Suarez et al. (2018). Usage on sugarcane and tangelos was reported in Suarez et al. (2018), but these use sites are no longer surveyed at the national level. Therefore, these crops are not presented in Table 3.

Table 2 summarizes average annual triazole and DMI fungicide usage by active ingredient from 2011 to 2015 and 2016 to 2020 in crop production. In terms of both pounds of active ingredient applied and BAT, propiconazole and tebuconazole remain the most heavily used active ingredients among the DMI fungicides on surveyed agricultural use sites. There has been no reported usage of triadimenol since publication of Suarez et al. (2018) and BEAD concludes that usage is likely minimal or nonexistent for this active ingredient. Ipconazole and triticonazole are registered for seed treatment uses, for which usage data are unavailable. Bromuconazole is registered for use in non-residential greenhouse production of roses only, a use for which usage data are unavailable. Recent usage data for imazalil and triforine were withheld by USDA NASS (2022) to avoid disclosing information for individual grower operations; while this suggests few growers apply these active ingredients, it is not necessarily indicative of low usage. Finally, due to the recent registration of mefentrifluconazole, the Agency lacks sufficient data to generate reliable estimates of usage. Thus, triadimenol, ipconazole, triticonazole, imazalil, triforine, bromuconazole, and mefentrifluconazole are not assessed herein.

Between 2016 and 2020, total agricultural DMI fungicide usage, in terms of base acres treated with the triazole and other DMI fungicides (BAT_{DMI}) and total pounds of DMI active ingredient (total lbs AI_{DMI}) applied, was higher than the previous reporting period (Table 2). Importantly, while BAT represents the total number of unique acres in the surveyed area that are treated with a specific active ingredient once, BAT_{DMI} may overestimate the number of unique acres treated with triazole and DMI fungicides, because multiple active ingredients may be applied to the same acre but data that would allow for a spatial analysis are not captured in pesticide usage surveys. Similarly, total lbs AI_{DMI} is the sum of pounds of active ingredient across all DMI fungicides applied. An average of 55.4 million BAT_{DMI} were treated with about 5.6 million total lbs AI_{DMI} annually from 2016 to 2020. For the DMI fungicide active ingredients with reported usage during both periods, this represents a 31% and 40% increase in average annual BAT_{DMI} and total lbs AI_{DMI} applied, respectively.

The increase in overall agricultural DMI fungicide usage is attributed to substantial increases in BAT_{DMI} for soybeans, corn, and wheat (Table 3). While TAT represents the total number of acre treatments that occurred, including multiple treatments to the same acre of cropland with an active ingredient, TAT_{DMI} describes the sum of TAT across the triazole and other DMI fungicide active ingredients. Since Suarez et al. (2018), total acres treated with DMI fungicides (TAT_{DMI}) increased from approximately 47.7 million to 61.0 million acres, respectively. This represents a 28% increase in TAT_{DMI}. The relatively similar rate of increase displayed for BAT_{DMI}, TAT_{DMI}, and total lbs AI_{DMI} between 2016 and 2020 and the previous reporting period suggests that overall usage of the triazole and other DMI fungicides in agricultural settings has increased in recent years and growers are generally making applications at rates similar to those used historically.

Table 2. Average annual agricultural usage of triazole and other DMI fungicides

Active Ingredient	2011-2015		2016-2020		Difference	
	Pounds AI	BAT_{DMI}	Pounds AI	BAT_{DMI}	Pounds AI	BAT_{DMI}
Propiconazole	1,600,000	17,000,000	2,200,000	22,000,000	600,000	4,500,000
Tebuconazole	1,100,000	7,200,000	1,400,000	9,900,000	300,000	2,700,000
Prothioconazole	450,000	6,400,000	750,000	8,800,000	300,000	2,400,000
Difenoconazole	180,000	1,700,000	400,000	3,500,000	220,000	1,800,000
Metconazole	280,000	6,900,000	290,000	6,100,000	10,000	-800,000
Myclobutanil	120,000	700,000	110,000	650,000	-10,000	-50,000
Triflumizole	98,000	260,000	77,000	190,000	-21,000	-70,000
Tetraconazole	48,000	800,000	74,000	980,000	26,000	180,000
Flutriafol	24,000	280,000	134,000	1,400,000	110,000	1,100,000
Cyproconazole	26,000	790,000	67,000	2,100,000	41,000	1,300,000
Fenbuconazole	40,000	250,000	34,000	210,000	-6,000	-40,000
Fenarimol	<5,000	30,000	<5,000	<5,000	NA	NA
All DMI Fungicides[1]	**4,000,000**	**42,000,000**	**5,600,000**	**55,000,000**	**1,600,000**	**13,000,000**

Sources: Kynetec 2021
1 Values may not sum due to rounding
NA: Not available
<5,000: Average reported usage of DMI fungicides was less than 5,000 lbs AI applied per survey year
Values averaged and rounded to protect proprietary nature of the data

As noted above, comparison of pounds applied across chemicals, even within a class, can be misleading because pesticides have different biological activities and thus, different efficacious application rates. Therefore, changes in usage for individual chemicals on a use site must be considered. For example, at the crop level (*i.e.,* considering the single application rates of all triazole and DMI fungicide active ingredients for a given crop collectively), the data suggest that all the surveyed crops that are treated with these chemicals have been treated at a similar average single application rate from 2016 to 2020 relative to the previous reporting period. However, this crop-level trend doesn't capture usage patterns at the active ingredient level. Further evaluation of the average single application rates for the individual triazole and other DMI fungicide active ingredients applied to all the surveyed crops (*i.e.,* total TAT/lbs AI applied for a given chemical across all surveyed crops) indicates that five active ingredients displayed notable increases in average single application rates relative to the previous reporting period: prothioconazole (20%), metconazole (17%), tetraconazole (15%), triflumizole (15%), and flutriafol (14%). Among the individual crops treated with these five fungicides, apples and cherries treated with triflumizole experienced notable average single application rate increases: 10% and 9%, respectively. Several additional crops treated with prothioconazole, metconazole, tetraconazole, triflumizole, and flutriafol experienced moderate rate increases (<5%) from 2016 to 2020 which collectively drove up the average application rate for these active ingredients. While a few crops have been treated with considerably more DMI fungicide active ingredient per acre from 2016 to 2020 relative to 2011 to 2015, each of these crops represents <1% of TAT_{DMI} from 2016 and 2020 and the overall lbs of triazole and other DMI fungicide active ingredients applied per acre in agricultural settings has remained relatively stable in recent years.

Based on TAT_{DMI} from 2011 to 2015, peanut and rice were previously identified as high usage crops. Triazole and DMI fungicide usage on peanut has declined since the Suarez et al. (2018) analysis, both in terms of total lbs AI_{DMI} applied (-20%) and TAT_{DMI} (-30%), however the disproportionately large decrease in acreage indicates increased application rates and/or a shift in usage towards active ingredients with relatively higher application rates. The average application rate for each of the three DMI fungicides used to treat the majority of peanut acres—tebuconazole, propiconazole, and prothioconazole— has been stable since the previous evaluation. However, tebuconazole, which has maintained the highest reported average application rate among the DMI fungicides applied to peanuts from 2011 to 2020, 0.20 pounds active ingredient per acre (lbs AI/A), was applied to 70% of peanut acres treated with DMI fungicides from 2016 to 2020 versus 60% in the previous reporting period. From 2016 to 2020, prothioconazole surpassed propiconazole as the second highest usage DMI fungicide applied to peanuts, in terms of TAT. Prothioconazole was applied at 0.12 lbs AI/A, on average, compared to 0.08 lbs AI/A for propiconazole. Thus, the discrepancy between the decrease in TAT and lbs AI is accounted for by changes in the proportion of acres treated with DMI fungicide active ingredients with higher application rates than those applied in the previous reporting period.

Similarly, the average annual lbs AI_{DMI} applied to rice increased by nearly 40% over the previous reporting period, while TAT increased by less than 20% during the same time. This pattern is largely attributed to increasing usage of a single active ingredient, propiconazole, from 2016 to 2020 compared to the previous reporting period. The data indicate that from 2016 to 2020, over 200,000 more rice acres were treated with propiconazole, and at a marginally higher application rate, compared to the 2011 to 2015 period. From 2011 to 2015, the average application rate of propiconazole was 0.14 lbs AI/A compared to 0.16 lbs AI/A from 2016 to 2020. The increase in rice acres treated with propiconazole coupled with the increased average application rate for the active ingredient from 2016 to 2020 resulted in a nearly 40% increase in pounds of propiconazole active ingredient applied to rice acreage relative to the 2011 to 2015 reporting period. Propiconazole was applied to nearly all rice acres treated with DMI fungicides during the most recent reporting period.

Between reporting periods, average annual TAT_{DMI} increased by over 13,000,000 acres. Data from 2016 to 2020 indicate a relatively modest change in agricultural usage of triazole and other DMI fungicides at the crop level relative to the previous reporting period (Table 3). Applications to wheat, corn, and soybeans accounted for 70% of total lbs AI_{DMI} applied and 80% of TAT_{DMI} on surveyed crops between 2016 and 2020. DMI fungicide usage remained greatest on wheat, which accounted for over 35% of lbs AI_{DMI} applied and 40% of BAT_{DMI} applied to surveyed agricultural crops. Corn and soybean usage accounted for an additional 35% and 45% of total lbs AI_{DMI} applied and BAT_{DMI}, respectively, from 2016 to 2020. In summary, there have been considerable increases in TAT_{DMI} among the high acreage crops: soybeans, corn, and wheat since the previous analysis (Table 3).

Table 3. Average annual DMI fungicide usage on agricultural crops

Use Site	2011-2015		2016-2020		Difference	
	Pounds AI	TAT	Pounds AI	TAT	Pounds AI	TAT
Almonds	90,000	740,000	170,000	1,400,000	80,000	660,000
Apples	80,000	510,000	70,000	500,000	-10,000	-10,000
Cantaloupe	<5,000	20,000	<5,000	10,000	NA	-10,000
Cherries	50,000	240,000	40,000	190,000	-10,000	-50,000
Corn	540,000	11,200,000	1,100,000	15,400,000	560,000	4,200,000
Cotton	10,000	100,000	40,000	260,000	30,000	160,000
Dry Beans/Peas	30,000	230,000	70,000	450,000	40,000	220,000
Grapefruit	10,000	80,000	<5,000	30,000	NA	-50,000
Grapes, Raisin	20,000	230,000	30,000	240,000	10,000	10,000
Grapes, Table	20,000	190,000	20,000	210,000	0	20,000
Grapes, Wine	90,000	850,000	120,000	1,100,000	30,000	250,000
Oranges	10,000	90,000	10,000	120,000	0	30,000
Peaches	10,000	120,000	10,000	80,000	0	-40,000
Peanuts	570,000	3,800,000	460,000	2,800,000	-110,000	-1,000,000
Pears	10,000	40,000	10,000	30,000	0	-10,000
Pecans	40,000	370,000	40,000	330,000	0	-40,000
Pistachios	10,000	100,000	10,000	90,000	0	-10,000
Plums/Prunes	10,000	70,000	10,000	60,000	0	-10,000
Potatoes	40,000	370,000	20,000	210,000	-20,000	-160,000
Rice	180,000	1,300,000	250,000	1,500,000	70,000	200,000
Soybeans	300,000	5,100,000	830,000	10,200,000	530,000	5,100,000
Strawberries	10,000	80,000	10,000	90,000	0	10,000
Sugar Beets	100,000	800,000	180,000	1,400,000	80,000	600,000
Sweet Corn	30,000	290,000	10,000	180,000	-20,000	-110,000
Tomatoes	20,000	230,000	10,000	190,000	-10,000	-40,000
Walnuts	10,000	40,000	30,000	190,000	20,000	150,000
Watermelons	20,000	110,000	10,000	90,000	-10,000	-20,000
Wheat, Spring	840,000	10,400,000	970,000	11,700,000	130,000	1,300,000
Wheat, Winter	820,000	9,500,000	1,000,000	11,600,000	180,000	2,100,000
All Crops[1]	**4,000,000**	**47,700,000**	**5,600,000**	**61,000,000**	**1,600,000**	**13,300,000**

Sources: Kynetec 2021
1 Includes low usage crops and crops with negligible change between reporting periods excluded from Table 3
NA: Not available
<5,000: Average reported usage of DMI fungicides was less than 5,000 lbs AI applied per survey year
Values averaged and rounded to protect proprietary nature of the data

Non-agricultural Usage

Surveys of the numerous non-agricultural uses of pesticides are limited in terms of frequency and scope, and many uses are not captured in nationally representative surveys. The available information for non-agricultural uses of the triazole and DMI fungicides is summarized below.

Recent nonagricultural market research data (NMRD) suggest that the total annual consumption of DMI fungicides by consumers has decreased considerably from an estimated 360,000-500,000 pounds in 2012 (Suarez et al. 2018) to less than 100,000 pounds in 2019 (NMRD 2020). This decline can be attributed to the cancellation of triforine and a considerable decline in usage of myclobutanil. Since Suarez et al. (2018), propiconazole usage has emerged in the consumer market, with an average of 34,000 pounds applied annually, but no triazole or other DMI fungicide active ingredient appears to have replaced triforine or myclobutanil, in terms of pounds of active ingredient applied, in the consumer sector (Kline 2017a, NMRD 2020). This could be attributed to differing maximum allowable application rates between the active ingredients; however, these application rates were not evaluated in this assessment. Triticonazole has been mentioned in recent consumer studies but because usage of this active ingredient, in pounds alone, does not constitute a substantial portion of overall usage in the sector, the data for triticonazole are not quantified in the usage reports (Kline 2017a, NMRD 2020). Non-agricultural market research indicates that tebuconazole, along with sulfur and copper, is one of the most widely used fungicides by consumers in lawn and garden products, however, quantitative usage data are not provided in the study (NMRD 2020).

In 2016, propiconazole represented about 12% of the wood preservative market (Kline 2017b). Nearly 70% of hard wood treated to prevent sapstain was treated with a blend of iodopropynyl butylcarbamate (IPBC) and propiconazole in 2016 and it is estimated that over 21 million lbs of propiconazole were applied in wood preservation applications that year (Kline 2017b). Of the propiconazole wood preservation applications, approximately 2% of pounds applied were for industrial uses, while the remaining 98% of pounds were applied for residential uses, including wood used in play-structures, decks, picnic tables, landscaping timbers, residential fencing, patios, and walkways/boardwalks (Kline 2017b).

More recent national-level pesticide usage data in the floriculture and nursery sectors, turf and ornamentals, and other specialty uses of the DMI fungicides are not available. Therefore, BEAD cannot provide an estimate of triazole and DMI fungicide usage in these areas.

DMI FUNGICIDE RESIDUE DETECTION VIA FOOD COMMODITIES

The Agency updated the residue detection values for triazole and DMI fungicides that were reported in Suarez et al. (2018) and that could be used to inform dietary assessments which estimate the potential of DMI fungicide exposure via residues on food commodities and in water. EPA is including information on residues via food commodities to aid CDC's epidemiological investigation. The percentage of samples with detectable triazole and other DMI fungicide residues across all sampled commodities remained relatively stable. From 2016 to 2020 1.6% of samples had detectable triazole and DMI fungicide residues compared to 1.5% from 2011 to 2015 (USDA Agricultural Marketing Service [AMS] 2022). However, while the percent of samples with detectable triazole and DMI fungicide residues across all commodities remained consistent, the highest average percent of detections for an individual commodity increased. From 2011 to 2015, the highest average percent of detections for any single commodity was less than 5% (Suarez et al. 2018). This value exceeded 5% for cherries (10.0%), frozen cherries (9.6%), grapefruit (5.5%), grapes (9.8%), hot peppers (5.7%), oranges (7.7%), raisins (24.8%), and tangerines (7.8%) from 2016 to 2020 (USDA AMS 2022). While residues may occur below levels of detection or quantification, those commodities with the highest proportion of detects may be of greatest interest to CDC.

CONCLUSIONS

At the request of CDC, BEAD is providing an update to the Suarez et al. (2018) analysis of triazole and DMI fungicide use and usage. Since the previous analysis, overall agricultural usage of the triazole and DMI fungicides, in terms of pounds of active ingredient applied and acres treated, has increased, with considerable increases in corn, soybean, and wheat TAT. Two additional sites, peanuts and potatoes, were previously among the highest usage crops in terms of TAT. DMI fungicide usage on rice increased marginally since the previous reporting period, however, decreased DMI usage is noted for peanut. While application rates remained relatively stable for most active ingredient x crop scenarios, notable rate increases were reported for apples and cherries treated with triflumizole from 2016 to 2020 relative to the previous reporting period. Consumer usage of the triazole and other DMI fungicides—particularly myclobutanil—has decreased substantially. BEAD notes that tebuconazole is considered and important fungicide for consumer products and that a considerable amount of propiconazole active ingredient is applied for wood preservation purposes. Although the likelihood that triazole and DMI fungicide residues from food commodities may contribute significantly to overall dietary exposure appears to be very low, epidemiological investigations of azole resistance development via dietary pathways might focus on those commodities with the highest potential for residues. Importantly, the data presented herein alone are not sufficient to link triazole resistance in *A. fumigatus* to any pesticidal use or uses. Rather, the information is intended to inform epidemiological investigations into the origins of clinical triazole resistance in *A. fumigatus*.

REFERENCES

Berger S., El Chazli Y., Babu AF., and Coste AT. (2017). Azole Resistance in Aspergillus fumigatus: A Consequence of Antifungal Use in Agriculture? Frontiers in Microbiology, 8, 1024. doi: 10.3389/fmicb.2017.01024

Chowdhary A, Kathuria S, Xu J, Meis JF (2013) Emergence of Azole-Resistant *Aspergillus fumigatus* Strains due to Agricultural Azole Use Creates an Increasing Threat to Human Health. PLoS Pathog 9(10): e1003633. https://doi.org/10.1371/journal.ppat.1003633

Denning DW, Venkateswarlu K, Oakley KL, Anderson MJ, Manning NJ, Stevens DA, Warnock DW, and Kelly SL. (1997). Itraconazole Resistance in Aspergillus fumigatus. Antimicrobial Agents and Chemotherapy, 41(6), 1364-1368.

Doki, T., Toda, M., Hasegawa, N., Hohdatsu, T. Takano, T., 2020. Therapeutic effect of an anti-human-TNF-alpha antibody and itraconazole on feline infectious peritonitis. Archives of Virology, 165, 1197-1206. https://doi.org/10.1007/s00705-020-04605-7

Fungicide Resistance Action Committee (FRAC). 2022. FRAC Code List ©2022: Fungal control agents sorted by cross resistance pattern and mode of action (including coding for FRAC Groups on product labels). Available at: https://www.frac.info/docs/default-source/publications/frac-code-list/frac-code-list-2022--final.pdf?sfvrsn=b6024e9a_2.

Garcia-Rubio, R. Gonzalez-Jimenez, I., Lucio, J., and Mellado, E. (2021). Aspergillus fumigatus Cross-Resistance between Clinical and Demethylase Inhibitor Azole Drugs. Applied and Environmental Microbiology, 87(5), 1-12.

Guillot, J. and Bond R. 2020. Malassezia Yeasts in Veterinary Dermatology: An Updated Overview. Frontiers in Cellular and Infection Microbiology, 10(79). doi: 10.3389/fcimb.2020.00079

Hagiwara, D., Watanabe, A., Kamei, K., & Goldman, G. H. (2016). Epidemiological and Genomic Landscape of Azole Resistance Mechanisms in *Aspergillus* Fungi. *Frontiers in microbiology*: 7 (1382). https://doi.org/10.3389/fmicb.2016.01382

Kano R, Kohata E, Tateishi A, Murayama SY, Hirose D, Shibata Y, Kosuge Y, Inoue H, Kamata H, Hasegawa A. (2015). Does farm fungicide use induce azole resistance in Aspergillus fumigatus? Med Mycol., 2015 (Feb 1), 53(2), 174-7. doi:10.1093/mmy/myu076.

Kline and Company. 2017a. Consumer Markets for Pesticides and Fertilizers 2016: U.S. Market Analysis and Opportunities - Volume 2. [Accessed April 2022].

Kline and Company. 2017b. Specialty Biocides Database. [Accessed May 2022].

Kynetec USA, Inc. 2021. "The AgroTrak® Study from Kynetec USA, Inc." iMap Software. Database Subset: 2016-2020. [Accessed April 2022].

Nonagricultural Market Research Data (NMRD). 2020a. Study on consumer markets for pesticides and fertilizers. [Accessed April 2022].

Nonagricultural Market Research Data (NMRD). 2020b. Study on global biopesticides. [Accessed August 2021].

Ribas e Ribas AD, Spoltib P, Del Ponte EM, Donatoc KZ, Schrekkerc H, Fuentefria AM. 2016. Is the emergence of fungal resistance to medical triazoles related to their use in the agroecosystems? A mini review. Brazilian Journal of Microbiology, 47(4), 793-799. doi: 10.1016/j.bjm.2016.06.006

Suarez, M. Alsadek, J., Chandgoyal, T. 2018. EPA Memorandum: Uses and Usage of Triazole and DeMethylation Inhibitor (DMI) Fungicide Pesticides.

United States Department of Agriculture National Agricultural Statistics Service (USDA NASS). 2022. QuickStats. Database Subset: 2017-2020. Available at: https://quickstats.nass.usda.gov/ [Accessed April 2022].

United States Department of Agriculture Agricultural Marketing Service (USDA AMS). 2022. Pesticide Data Program. Database Subset: 2016-2020. Available at: https://www.ams.usda.gov/datasets/pdp [Accessed April 2022].